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FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER LLP
1300 I STREET, NW
WASHINGTON, DC 20005

EXAMINER	
HUYNH, PHUONG N	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 03/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/803,918	DAYER ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12/23/04*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-61* is/are pending in the application.

4a) Of the above claim(s) *1-8,11-14,18-35,44,45 and 50-61* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9,10,15-17,36-43 and 46-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 August 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Notice to comply*.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/23/03 has been entered.

2. Claims 1-61 are pending.

3. Claims 1-8, 11-14, 18-35, 44-45, and 50-61 stand withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

4. Claims 9-10, 15-17, 36-43, and 46-49 are being acted upon in this Office Action.

5. Applicant is advised that should claim 9 be found allowable, claim 10 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

6. Claims 9-10, and 15-16 are object to because "apo-A-1" should have been "apo-A-I".

7. The drawings were received on 8/17/2001. These replacement drawings will replace the drawings submitted on 3/13/01. However, color photographs and color drawings are acceptable only for examination purposes unless a petition filed under 37 CFR 1.84(a)(2) is granted permitting their use as acceptable drawings. In the event that applicant wishes to use the drawings currently on file as acceptable drawings, a petition must be filed for acceptance of the color photographs or color drawings as acceptable drawings. Any such petition must be accompanied by the appropriate fee set forth in 37 CFR 1.17(h), three sets of color drawings or color photographs, as appropriate, and, unless already present, an amendment to include the

following language as the first paragraph of the brief description of the drawings section of the specification:

The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

Color photographs will be accepted if the conditions for accepting color drawings have been satisfied.

8. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821 (a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/or Amino Acid Sequence Disclosure.

This application fails to comply with the sequence rules because SEQ ID NO is required in FIG. 1C-D. Appropriate correction is required.

9. The disclosure is objected to because of the following informalities. "(Fig. 6, B and C)" on page 98, line 28 does not match the description for SDS-PAGE that has Mr = 28,000 and Mr =18,000 bands. "(Fig. 6, B and C)" should have been "FIG 7 E)". Likewise, the "(Fig. 6E)" on page 99, line 2 and "(Fig. 6E, lane c)" on page 99, line 8 do not match with the Western blot analysis. It should have been "FIG. 7E, lane c". It is noted that FIGS. 6B-F are flow cytometry data and not Western blot analysis (FIG. 7E). The only Figure that fits Western blot analysis is Figure 7E. Further, it is noted that "(Fig. 7A)" on page 99, line 17 should have been "(FIG. 6A)", "(Fig. 7B)" on page 99, line 24 should have been "(FIG. 6B)", "(Fig. 7C)" on page 99, line 26 should have been "FIG. 6C)"; "(Fig. 7, D and E) on page 99, lines 28-29 should have been "(FIG. 6D and E)" and "(Fig. 7F) on page 100, line 1 should have been "(FIG. 6F)". Appropriate action is required.

10. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 9-10, 15-17, 36-43 and 46-49 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) an isolated apo-A-I polypeptide comprising SEQ ID NO: 2 and an apo-A-I fragment consisting of amino acid residues 25 to 194 of SEQ ID NO: 2 for inhibiting T cell signaling of monocyte for IL-1β and TNFα production in vitro, (2) a composition comprising an isolated apo-A-I polypeptide comprising SEQ ID NO: 2 or an apo-A-I fragment consisting of amino acid residues 25 to 194 of SEQ ID NO: 2 and a pharmaceutically acceptable carrier for inhibiting T cell signaling of monocyte for IL-1β and TNFα production, and (3) a fusion polypeptide comprising SEQ ID NO: 2 or an apo-A-I fragment consisting essentially of amino acid residues 25 to 194 of SEQ ID NO: 2 and a heterologous polypeptide selected from the group consisting of IgG constant domain, an alkaline phosphatase, a tat protein, or a FLAG epitope for detection assays, **does not** reasonable provided enablement for any apo-A-I fragment T-cell activation inhibitor-like polypeptide fragment as set forth in claims 9-10, and 15-17 for regulates T-cell-mediated activation of monocytes, any polypeptide mentioned above is covalently modified (claims 40-43), any composition comprising any apo-A-I fragment T-cell activation inhibitor-like polypeptide fragment as set forth in claims 36-39 for treating any disease, and any fusion polypeptide comprising any apo-A-I fragment T-cell activation inhibitor-like polypeptide fragment and a heterologous amino acid sequence selected from an IgG constant domain, any fragment thereof, an alkaline phosphatase, or any fragment thereof, a tat protein or a FLAG epitope (claims 46-49) for any purpose. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims for the same reasons set forth in Paper No 13.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient

to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only human Apo-A-I comprising SEQ ID NO: 2 encoding by the polynucleotide of SEQ ID NO: 1. Only the human Apo-A1 fragment recovering from the fractions 23-26 with a molecular weight 28 kDa protein consisting of amino acid residues 25 to 194 of SEQ ID NO: 2 has inhibitory activity of T cell signaling of monocyte for IL-1β and TNFα production in vitro (See p7, Figure 4A-B).

The specification does not teach how to use make any polypeptide apo-A-I fragment produced by a process comprising culturing T a eukaryotic cell comprising a vector comprising any nucleic acid consisting essentially of *any* nucleotide sequence which hybridizes under "moderately or highly stringent conditions" to the complement of any nucleotide sequence as set forth in claims 1(a) through (h), or any nucleotide sequence that is at least about 70, 75, 80, 85, 90, 95, 96, 97, 98 or 99 identical to at least any one of nucleotide sequence in claim 1(a)-(j), or *any* nucleotide sequence encoding *any* allelic variant, *any* splice variant of nucleotide sequence in claim 1(a)-(j), any nucleotide sequence mentioned above encoding any polypeptide of at least about 25 amino acid residues, any nucleotide sequence mentioned above comprising any fragment of at least about 16 nucleotides, any nucleotide sequence complementary to any polynucleotide mentioned above, let alone the polypeptide regulates T cell-mediated activation of monocytes. There is insufficient guidance as to the structure of any apo-A-I fragment that has inhibitory T-cell-mediated activation of monocytes activity because the term "consisting essentially of" is open-ended. It expands the apo-A-I fragment to include additional amino acids at either or both ends. There is insufficient guidance as to which undisclosed amino acids to be include and whether the resulting apo-1 fragment could regulate T-cell-mediated activation of monocytes. Further, the term "regulates" could be stimulatory or inhibitory which are mutually exclusive. Beside the specific Apo-A-I polypeptide fragment consisting of amino acid residues 25 to 194 of SEQ ID NO: 2 that inhibits T cell signaling of monocyte for IL-1β and TNFα production, the other undisclosed polypeptide and polypeptide fragment do not inhibit T-cell-mediated monocyte signaling that lead to a reduction of IL-1β and TNFα production. Let alone a composition comprising any undisclosed apo-A1 fragment and a pharmaceutically acceptable formulation agent for treating all disease. Given the nucleotide sequences mentioned above are not adequately enabled, the complementary nucleotide sequence (claims 9(j), 10(j)) to any nucleotide sequence are not enabled.

With regard to apo-A-fragment produced by any nucleotide sequence which "hybridizes under moderately or highly stringent conditions" to the complement of any nucleotide sequence set forth in claims 9(i), 10(i), 16(a)(9), and 16(b)(9), the state of the prior art as exemplified by Wallace *et al*, of record, is such that determining the specificity of hybridization probes is empirical by nature and the effect of mismatches within an oligonucleotide probe is unpredictable. Further, a polynucleotide fragment hybridizing to any of the nucleotide sequence set forth in (a) through (h) of claims 9-10 under any conditions does not necessary encodes an apo-A-fragment that has the prerequisite activity such as inhibits or stimulates T-cell mediated activation of monocytes. Given the indefinite number of undisclosed apo-A fragment encoded by undisclosed polynucleotide, there is insufficient working example demonstrating any apo-A-I fragment could inhibit T-cell-mediated activation of monocytes, much less for treating any disease.

With regard to apo-A-fragment produced by any nucleotide sequence that is at least 70, 75, 80, 85, 90, 95, 96, 97, 98 or 99 % identical to at least any one of nucleotide sequence in claim 9(a)-(j) and 10(a)-(j), the specification fails to provide guidance as to how to make and use the claimed apo-A-I fragment produced by culturing host cell polynucleotide "is at least 70, 75, 80, 85, 90, 95, 96, 97, 98 or 99% identical to the claimed sequences set forth in part (a) through (j) of claims 9-10 part (a) through (c) of claim 15, part a of claim 16 using any computer program recited in claim 17. The use of "percent" in conjunction with any of the various terms that refer to sequence similarity is a problem since sequence identity between two sequences has no common meaning within the art. The term "percent" can be defined by the algorithm and parameter values set when using the algorithm used to compare the sequences. The scoring of gaps when comparing one sequence to another introduces uncertainty as to the percent of similarity between two sequences. Since the nucleic acid sequence of a polynucleotide determines its protein coding properties, predictability of which changes can be tolerated in a polynucleotide's nucleic acid sequence and still retain similar functions and properties requires a knowledge of, and guidance with regard to which nucleic acids in the nucleotide sequence, if any are tolerant of modification and which are conserved (ie., expectedly intolerant to modification), and detailed knowledge of the ways in which the product's structure relates to its functional usefulness. However, the problem of predicting functional aspects of the product from mere sequence data of a single nucleic acid sequence and what changes can be tolerated is complex and well outside the realm of routine experimentation. *In re Fisher*, 1666 USPQ 19 24 (CCPA 1970)

indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Without such guidance, the fragments which can be made and used to encode peptides of the claimed activity is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly extensive and undue. See *Amgen, Inc. v. Chugai Pharmaceutical Co. Ltd.*, 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991) at 18 USPQ2d 1026-1027 and *Ex parte Forman*, 230 USPQ 546 (BPAI 1986).

Attwood *et al*, of record, teach that protein function is context-dependent and the state of the art of making functional assignments merely on the basis of some degree of similarity between sequences and the current structure prediction methods is unreliable.

Skolnick *et al*, teach that squence-based methods for function prediction are inadequate and knowing a protein's structure does not necessary tell one it's function (See entire document, Abstract in particular).

It is known in the art that even single amino acid changes or differences in a protein's amino acid sequence can have dramatic effects on the protein's function. For example, Mikayama *et al*, teach that the human glycosylation-inhibiting factor (GIF) protein differs from human macrophage migration inhibitory factor (MIF) by a single amino acid residue (Figure 1 in particular). Yet, Mikayama *et al* teach further that GIF is unable to carry out the function of MIF and MIF does not demonstrate GIF bioactivity (Abstract in particular). It is also known in the art that a single amino acid change in a protein's sequence can drastically affect the structure of the protein and the architecture of an entire cell. Until a specific function or activity of the Apo-A-I fragment encoded by polycleotide that is at least 70, 75, 80, 85, 90, 95, 96, 97, 98 or 99 % identical to at least any one of nucleotide sequences set forth in part (a) through (j) of claims 9-10 part (a) through (c) of claim 15, part a of claim 16, any allelic variants (claims 9(i), claim 10, 16) or splice variants (claim 10 (i)), which fragment of any ortholog of SEQ ID NO: 2 (Claim 15) thereof are identified and has a specific function, the specification as filed merely extends an invention for one skill in the art for further experimentation.

With regard to apo-A-fragment produced by polynucleotide such as the ones recited in claim 9(n), claim 10(m), claim 15 (e), and claim 16(c) "comprising" a fragment of at least about 16 nucleotides, the term "comprising" is open-ended. It expands the nucleotide to include additional nucleotide to either or both ends of polynucleotide. So long the polynucleotide is at least 16 nucleotides in length, which is about 5 amino acids, the length of the polynucleotide could be to any length. There is insufficient guidance as to the structure and functions of the apo-

A-fragment encoded by the undisclosed polynucleotide. Further, there is insufficient in vivo working example demonstrating that all Apo-A-I fragments is effective for regulating T-cell-mediated activation of monocytes, in turn, useful for treating all disease.

With regard to apo-A-I fragment produced by any nucleotide set forth in claims 9(m), 10 (m), 15 (h), 16(c) encoding any polypeptide of at least about 25 amino acid residues, not only the allelic variant and nucleotide sequence that is at least 70, 75, 80, 85, 90, 95, 96, 97, 98 or 99 % identical to the claimed polynucleotide encoding SEQ ID NO: 2 and fragment thereof have not been identified, there is insufficient guidance as to which 25 amino acids within the full length undisclosed polypeptide, and the corresponding polynucleotide have regulatory activity such as inhibiting T-cell-mediated activation of monocytes for IL-1β and TNFα production.

Since the apo-A-fragment, the corresponding nucleotide sequence mentioned above are not enabled, it follows that any composition comprising any undisclosed apo-A-fragment for treating all disease is not enabled. It also follows that all undisclosed apo-A-I fragment which is covalently modified (claims 40-43) are not enabled. Given the lack of guidance as to the structure and function of any undisclosed the apo-A-fragment, the fusion polypeptide comprising said undisclosed apo-A-I fragment to any IgG constant domain, alkaline phosphatase, tat protein and FlAG epitope is not enabled. Further, there is insufficient guidance as to which "fragment thereof" of IgG constant or alkaline phosphatase the undisclosed apo-A-I fragment fused to.

Even if the apo-A-fragment limited to the 28 kDa protein consisting of amino acid residues 25 to 194 of SEQ ID NO: 2, there is no in vivo working example that the claimed apo-A-I fragment could treat any disease. A pharmaceutical composition (claims 36-39) in the absence of in vivo data are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the polypeptide fragment unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

For these reasons, it would require undue experimentation even for one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments filed 12/23/03 have been fully considered but are not found persuasive.

Applicants' position is that (1) claims 9, 10, 15 and 16 have been amended. Claim 16 is also amended to recite certain exemplary hybridization conditions that are described as "highly stringent conditions" and "moderately stringent condition" in the specification page, 21, lines 11-18, and page 22, lines 16-19. claims 46 and 48 are amended to recite certain specific heterologus amino acid sequences, see page 33, lines 8-9 for IgG constant domain, page 60, line 10 for alkaline phosphatase, page 65, lines 15-16 for tat protein, page 103, lines 28-29 for FLAG epitope.

However, the amended claims still have the same problems as before. Specifically, there is insufficient guidance as to the structure and function of any apo-A-I fragment that "regulates" T-cell-mediated activation of monocytes, let alone for treating all disease. The specification discloses only human Apo-A-I comprising SEQ ID NO: 2 encoding by the polynucleotide of SEQ ID NO: 1. Only the human Apo-A-I fragment recovering from the fractions 23-26 with a molecular weight 28 kDa protein consisting of amino acid residues 25 to 194 of SEQ ID NO: 2 has inhibitory activity of T cell signaling of monocyte for IL-1β and TNFα production in vitro (See p7, Figure 4A-B). Beside the specific Apo-A-I polypeptide fragment consisting of amino acid residues 25 to 194 of SEQ ID NO: 2 that inhibits T cell signaling of monocyte for IL-1β and TNFα production, the other undisclosed Apo-A-I fragments, and the corresponding polynucleotides, allelic variants, splice variants, otholog, nucleotide sequence that is at least about 70, 75, 80, 85, 90, 95, 96, 97, 98 or 99 identical to at least any one of nucleotide sequences, and amino acid sequence that is at least about 70, 75, 80, 85, 90, 95, 96, 97, 98 or 99 identical to at least any one of amino acid sequences do not inhibit T-cell-mediated monocyte signaling that lead to a reduction of IL-1β and TNFα production. There is insufficient guidance as to which amino acids within the full-length undisclosed polypeptide, and polynucleotides mentioned above could regulate T-cell mediated activation of lymphocytes. Given the indefinite number of apo-A-

I fragment and corresponding nucleotides, there is insufficient working examples demonstrating that all apo-A-I is effective for regulating T-cell-mediated activation of monocytes, such as inhibiting T cell signaling of monocyte for IL-1β and TNFα production, let alone a composition comprising any undisclosed apo-A1 fragment and a pharmaceutically acceptable formulation agent for treating all disease. Applicant is directed to the detailed explanation discussed supra.

13. Claims 9-10, 15-17, 36-43 and 46-49 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of any apo-A-I fragment such as the ones recited in claims 9-10, 15-17, 36-43 and 46-49 wherein said apo-A-I fragment regulates T-cell-mediated activation of monocytes because of the following reasons.

The specification discloses only human Apo-A-I comprising SEQ ID NO: 2 encoding by the polynucleotide of SEQ ID NO: 1. Only the human Apo-A1 fragment recovering from the fractions 23-26 with a molecular weight 28 kDa protein consisting of amino acid residues 25 to 194 of SEQ ID NO: 2 has inhibitory activity of T cell signaling of monocyte for IL-1β and TNFα production in vitro (See p7, Figure 4A-B).

Other than the specific human Apo-A-I fragment consisting of amino acid residues 25 to 194 of SEQ ID NO: 2 that has inhibitory activity of T cell signaling of monocyte for IL-1β and TNFα production, there is adequate written description about the structure associated with function without the specific nucleotide sequence, and the corresponding amino acid sequence since the term "consisting essentially of" is open-ended. It expands the nucleic molecule encoding the apo-A-I fragment to include additional nucleotides at either or both ends. Further, there is inadequate written description about which apo-A-I fragment produced by a process culturing eukaryotic cell comprising a vector comprising any nucleic acid molecule such as the ones recited in claim 9(a)-(h), 10(a)-(h) or which apo-A-I fragment such as the ones recited in claims 15(a)-(e), or the ones encoded by nucleic acid molecule in claim 16(a) could regulate T-cell-mediated activation of monocytes. The term "regulates" could be inhibitory or stimulatory which are mutually exclusive. The specification only the specific apo-A-I fragment inhibits T cell signaling of monocyte for IL-1β and TNFα production. The specification has not described which apop-A-1 fragment stimulates T-cell-mediated activation of monocytes, for example.

Given the nucleotide sequence mentioned above is not adequately described, the complementary nucleotide sequence to any nucleotide sequence is not adequately described.

With regard to apo-A-fragment produced by any nucleotide sequence which "hybridizes under moderately or highly stringent conditions" to the complement of any nucleotide sequence set forth in claims 9(i), 10(i), 16(a)(9), and 16(b)(9), any nucleotide fragment could hybridize to the claimed nucleotide sequences that encoded the apo-A-I fragment. However, not all nucleotide sequences that hybridize to the claimed sequence have the regulatory function. There is inadequate written description about the structure associated with function without the nucleotide sequence. There is inadequate written description about which nucleotide fragment within the full-length of any nucleotide sequence of SEQ ID NO: 1 has the specific function such as inhibiting T-cell signaling of monocyte for IL-1β and TNFα production or stimulating T cell signaling, much less for using all undisclosed apo-A-I fragment encoded by the undisclosed polynucleotide for treating all disease. Given the indefinite number of undisclosed polynucleotide, the apo-A-I fragments encoded by the undisclosed nucleotide that could inhibit T-cell-mediated activation of monocytes are not adequately described, let alone for a composition for treating all disease.

With regard to apo-A-fragment produced by any nucleotide sequence that is at least 70, 75, 80, 85, 90, 95, 96, 97, 98 or 99 % identical to at least any one of nucleotide sequence in claims 9(k), 10(k), 15(g), 16(a), any nucleotide sequence encoding any allelic variant or splice variant (claims 9(l), 10(l), 16(b)), any otholog of SEQ ID NO: 2 (Claim 15(f)), the use of "percent" in conjunction with any of the various terms that refer to sequence similarity is a problem since sequence identity between two sequences has no common meaning within the art. The term "percent" can be defined by the algorithm and parameter values set when using the algorithm used to compare the sequences. The scoring of gaps when comparing one sequence to another introduces uncertainty as to the percent of similarity between two sequences. Since the nucleic acid sequence of a polynucleotide determines its protein coding properties, predictability of which changes can be tolerated in a polynucleotide's nucleic acid sequence and still retain similar functions and properties requires a knowledge of, and guidance with regard to which nucleic acids in the nucleotide sequence, if any are tolerant of modification and which are conserved (ie., expectedly intolerant to modification), and detailed knowledge of the ways in which the product's structure relates to its functional usefulness. However, the problem of predicting functional aspects of the product from mere sequence data of a single nucleic acid

sequence and what changes can be tolerated is complex and well outside the realm of routine experimentation. There is inadequate written description about the structure associated of any nucleotide sequence that is at least 70, 75, 80, 85, 90, 95, 96, 97, 98 or 99 % identical to at least any one of nucleotide sequence in claims 9(k), 10(k), 15(g), 16(a), any nucleotide sequence encoding any allelic variant or splice variant (claims 9(l), 10(l), 16(b)), any otholog of SEQ ID NO: 2 (Claim 15(f)) that inhibit T cell signaling of monocyte for IL-1β and TNFα production. Until a specific function or activity of the Apo-A-I fragment encoded by a polycleotide that is at least 70, 75, 80, 85, 90, 95, 96, 97, 98 or 99 % identical to at least any one of nucleotide sequences set forth in part (a) through (j) of claims 9-10 part (a) through (c) of claim 15, part a of claim 16, any allelic variants (claims 9(i), claim 10, 16) or splice variants (claim 10 (i)), which fragment of any ortholog of SEQ ID NO: 2 (Claim 15) thereof are identified and has a specific function, the specification as filed merely extends an invention for one skill in the art for further experimentation and thus said undisclsoed Apo-A-I fragment is not adequately described.

With regard to apo-A-I fragment produced by any nucleotide set forth in claims 9(m), 10 (m), 15 (h), 16(c) encoding any polypeptide of at least about 25 amino acid residues, not only the allelic variant and nucleotide sequence that is at least 70, 75, 80, 85, 90, 95, 96, 97, 98 or 99 % identical to the claimed polynucleotide encoding SEQ ID NO: 2 and fragment thereof have not been identified, there is insufficient written description about which 25 amino acids within the full length undisclosed polypeptides mentioned above and the corresponding polynucleotide sequence have regulatory function such as inhibiting T-cell-mediated activation of monocytes for IL-1β and TNFα production.

With regard to apo-A-fragment produced by polynucleotide such as the ones recited in claim 9(n), claim 10(m), claim 15 (e), and claim 16(c) "comprising" a fragment of at least about 16 nucleotides, the term "comprising" is open-ended. It expands the nucleotide to include additional nucleotide to either or both ends of polynucleotide. So long the polynucleotide is at least 16 nucleotides in length, which is about 5 amino acids, the length of the polynucleotide could be any length. There is insufficient written about the other undisclosed amino acids and the corresponding nucleotides for the apo-A-I fragment set forth in claims claim 9(n), claim 10(m), claim 15 (e), and claim 16(c). Since the apo-A-fragment, the corresponding nucleotide sequence mentioned above are not adequately described, it follows that any composition comprising any undisclosed apo-A-fragment for treating all disease are not adequately described (claims 36-39). It also follows that all undisclosed apo-A-I fragment which is covalently modified (claims 40-43)

are not adequately described. Given the lack of guidance as to the structure and function of any undisclosed the apo-A-fragment, the fusion polypeptide comprising said undisclosed apo-A-I fragment to any IgG constant domain, alkaline phosphatase, tat protein and FlAG epitope are not adequately described. Further, there is insufficient written description about which "fragment thereof" of IgG constant or alkaline phosphatase the undisclosed apo-A-I fragment fused to.

Even if the apo-A-fragment limited to the 28 kDa protein consisting of amino acid residues 25 to 194 of SEQ ID NO: 2, there is no in vivo working example that the claimed apo-A-I fragment could treat any disease.

Finally, the specification discloses only the human Apo-A1 fragment recovering from the fractions 23-26 with a molecular weight 28 kDa protein consisting of amino acid residues 25 to 194 of SEQ ID NO: 2 has inhibitory activity of T cell signaling of monocyte for IL-1β and TNFα production in vitro (See p7, Figure 4A-B). Given the lack of a written description of *any* additional representative species of Apo-A-I fragment that regulates T-cell-mediated activation of monocytes for treating all disease, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments filed 12/23/03 have been fully considered but are not found persuasive.

Applicants' position is that (1) claims 9, 10, 15 and 16 have been amended. Claim 16 is also amended to recite certain exemplary hybridization conditions that are described as "highly stringent conditions" and "moderately stringent condition" in the specification page, 21, lines 11-18, and page 22, lines 16-19. claims 46 and 48 are amended to recite certain specific heterologus amino acid sequences, see page 33, lines 8-9 for IgG constant domain, page 60, line 10 for alkaline phosphatase, page 65, lines 15-16 for tat protein, page 103, lines 28-29 for FLAG epitope.

However, the amended claims still have the same problems as before. Applicant is directed to the detailed explanation discussed supra.

14. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

15. Claims 9, 10, 15, 17, 36, 38, 40-41, and 46-47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The "apo-A-1 fragment...comprising a nucleic acid molecule *consisting essentially of* a nucleotide sequence ...*comprising* a fragment of at least about 16 nucleotides in Claims 9(n), and 10(n) is ambiguous, indefinite and improper since it is not clear if the nucleotide sequence is referring to a fragment comprising at least about 16 nucleotides derived from nucleotide sequence selected from (k), (l) and (m) or a nucleotide sequence selected from one of (k), (l) and (m). One of ordinary skill in the art cannot appraise the metes and bound of the claimed invention.

The "apo-A-1 fragment T-cell activation inhibitor like polypeptide *consisting essentially of* ...a fragment of the amino acid sequence set forth in at least one of (a), (b), (c), (d) or (e) comprising at least about 25 amino acid residues...monocytes in claim 15(h) is ambiguous, indefinite and improper since it is not clear if the fragment the same fragment in (a), (b), (c), (d) and (e) or a fragment derived from (a), (b), (c), (d) and (e) having at least about 25 amino acid residues from (a), (b), (c), (d) and (e), respectively. One of ordinary skill in the art cannot appraise the metes and bound of the claimed invention.

16. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

17. Claims 15, 36 and 38 are rejected under 35 U.S.C. 102(b) as being anticipated by Curtis *et al* (J Biol Chem 263(27): 13779-13785, 1988, PTO 892).

Cutis et al teach various isolated apo-A-I fragments consisting essentially of an amino acid sequence such as EMSKDLEEVYAKVQPYLDDFQKKWQEEMELYRQKVE of the full-length human apop-A-1 (See page 13782, column 2, in particular). The said apo-A-1 fragment is at least 25 amino acids in length. The term "consisting essentially of" is open-ended. It expands the claimed apo-A-1 fragment from residues 73 to 113 to include additional amino acids at either or both ends to include the reference fragment. Cutis et al further teach an apo-A-1 fragment consisting essentially of DEPPQSPWDRVKDLATVYVDVLK, which is about 25 amino acids in length. Cutis et al further teach a composition comprising the reference apo-A-I fragment and a pharmaceutical acceptable carrier such as phosphate saline buffer (See page 13780, column 1, synthesis of peptides, in particular). Since the refrence apo-A-I fragments appear to be identical to the claimed apo-A-I fragments, the functional property such as " regulates T-cell-mediated activation of monocytes" would be an inherent property of the reference apo-A-I fragments. Since the Patent Office does not have the facilities for examining and comparing the antibodies of the instant invention to those of the prior art, the burden is on applicant to show that the prior art antibody is different from the claimed antibody. See In re Best, 562 F.2d 1252, 195 USPQ 430(CCPA 1977). Thus, the reference teachings anticipate the claimed invention.

18. Claims 9-10, 15-16, and 36-39 are rejected under 35 U.S.C. 102(b) as being anticipated by US Pat No 5,721,114, (Feb 24, 1998, PTO 892).

The '114 patent teaches an Apo-A-I fragment produced by a process of culturing host cell comprising a vector comprising a nucleic acid molecule consisting essentially a nucleotide sequence encoding an allelic variant of nucleotide sequence which hybridizes under moderately or highly stringent condition to the complement of nucleotide sequence encoding a polypeptide from 156 to 267 of SEQ ID NO: 2 (See column 10, lines 9-66, see reference SEQ ID NO: 6, Fig 4, in particular). The reference human Apo-A-IM is a natural variant of the claimed Apo-A-I that differs only having the amino acid Arg173 replaced with the amino acid Cys 173 or the codon CGC changed to TGC (See column 1, lines 49-58, in particular). The reference nucleotide sequence (SEQ ID NO: 5) encoding the reference Apo-AI-M would hybridize to the claimed nucleic acid sequence given that there is only one codon difference. The reference Apo-A-I fragment is a 59 residues C terminal fragment (residues 185-243 of SEQ ID NO: 6), which

comprises at least 25 amino acids in length (See column10, lines 63-64, Figure 4, in particular). The term "consisting essentially of" is open-ended. It expands the claimed fragment to include additional amino acids, the corresponding nucleotides at either or both ends to include the reference fragment. With regard to produced eukaryotic cells, a product is a product, irrespective of how the product is made. The '114 patent further teaches a composition comprising the reference Apo AI-M fragment and a pharmaceutical acceptable carrier such as sodium phosphate buffer (See column 10, line 56, in particular). The '114 patent further teaches fusion polypeptide wherein the reference Apo AI moiety is fused to the one or more IgG binding domain of protein A or beta galactosidase (See column 2, lines 10-13, in particular). Given the refrence apo-A-I fragment appears to be identical to the claimed apo-A-I fragments, the functional property such as " regulates T-cell-mediated activation of monocytes" would be an inherent property of the reference apo-A-I fragment. Since the Patent Office does not have the facilities for examining and comparing the antibodies of the instant invention to those of the prior art, the burden is on applicant to show that the prior art antibody is different from the claimed antibody. See In re Best, 562 F.2d 1252, 195 USPQ 430(CCPA 1977). Thus, the reference teachings anticipate the claimed invention.

19. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

20. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

21. Claims 15 and 46-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Curtis *et al* (J Biol Chem 263(27): 13779-13785, 1988, PTO 892) in view of US Pat 5,116,964 (May 1992; PTO 892) and US 5,408,038 (of record).

The teachings of the Curtis et al have been discussed supra.

The claimed invention as recited in claims 46-47 differs from the teachings of the reference only that the fusion polypeptide wherein the heterologous amino acid sequence is an IgG constant or fragment thereof.

The '964 patent teaches immunoglobulin fusion polypeptide such as CH2 and CH3 domains of the constant region of an immunoglobulin or fragment thereof fused to any polypeptide of interest such as LHR (See abstract, column 10, lines 10-16, in particular). The advantage of immunoglobulin fusion polypeptide extends the half-lives of the fusion protein and useful in therapeutic or diagnostic (See column 8, lines 10-34, in particular).

The '038 patent teaches that apoA-I is unstable (see column 2, lines 6-8, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to fuse apo-A-I polypeptide fragment as taught by Curtis et al to the IgG constant domain or the CH2-CH3 fragment thereof as taught by the '964 patent for a fusion polypeptide comprising the Apo-A-I fragment and the constant region of an immunoglobulin or the CH2-CH3 fragment of IgG as taught by Curtis et al, the '038 patent and the '964 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the '038 patent teaches that apoA-I is unstable (see column 2, lines 6-8, in particular). The '964 patent teaches immunoglobulin fusion polypeptide extends the half-lives of the fusion protein and useful in therapeutic or diagnostic (See column 8, lines 10-34, in particular).

22. Claims 15-16, and 46-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No 5,721,114, (Feb 24, 1998, PTO 892) in view of US Pat 5,116,964 (May 1992; PTO 892).

The teachings of the '114 patent have been discussed supra. The '114 patent further teaches that Apo-AI-M is useful for protecting subjects from atherosclerosis (See column 1, lines 64-65, in particular).

The claimed invention as recited in claims 46-49 differs from the teachings of the reference only that the fusion polypeptide wherein the heterologous amino acid sequence is an IgG constant or fragment thereof.

The '964 patent teaches immunoglobulin fusion polypeptide such as CH2 and CH3 domains of the constant region of an immunoglobulin or fragment thereof fused to any polypeptide of interest such as LHR (See abstract, column 10, lines 10-16, in particular). The advantage of immunoglobulin fusion polypeptide extends the half-lives of the fusion protein and useful in therapeutic or diagnostic (See column 8, lines 10-34, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the IgG binding domain of protein A or beta galactosidase of the fusion polypeptide as taught by the '144 patent for the IgG constant domain or fragment thereof as taught by the '964 patent for a fusion polypeptide comprising the allelic variant of Apo-A-I fragment and the constant region of an immunoglobulin or the CH2-CH3 fragment of IgG as taught by the '114 and the '964 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the '964 patent teaches immunoglobulin fusion polypeptide extends the half-lives of the fusion protein and useful in therapeutic or diagnostic (See column 8, lines 10-34, in particular). The '114 patent teaches that Apo-AI-M is useful for protecting subjects from atherosclerosis (See column 1, lines 64-65, in particular).

23. Claims 15, 36, 38, 40 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Curtis *et al* (J Biol Chem 263(27): 13779-13785, 1988, PTO 892) in view of US Pat No. 5,824,784 (Oct 1998; PTO 892) and US 5,408,038 (of record).

The teachings of the Curtis et al have been discussed supra.

The claimed invention in claim 38 differs from the teachings of the reference only that composition wherein the pharmaceutically acceptable formulation agent comprises at least one of adjuvant, solubilizer, stabilizer or anti-oxidant.

The claimed invention as recited in claim 40 differs from the teachings of the reference only that polypeptide is covalently modified with a water-soluble polymer.

The claimed invention as recited in claim 41 differs from the teachings of the reference only that polypeptide is covalently modified with a water soluble polymer wherein the water soluble polymer is selected from polyethylene glycol, monomethoxy polyethylene glycol, dextran, cellulose, poly(N-vinyl pyrrolidone) polyethylene glycol, propylene glycol homopolymers, polypropylene oxide/ethylene oxide co-polymers, polyoxyethylated polyols and polyvinyl alcohol.

The '784 patent teaches method and composition for covalently modified any polypeptide of interest such as G-CSF or INF with a water-soluble polymer such as polyethylene glycol, monomethoxy polyethylene glycol, dextran, cellulose, poly(N-vinyl pyrrolidone) polyethylene glycol, propylene glycol homopolymers, polypropylene oxide/ethylene oxide co-polymers, polyoxyethylated polyols and polyvinyl alcohol (See abstract, column 6, lines 32-67 bridging column 7, lines 1-5, column 9, lines 64-66, in particular). The '784 patent further teaches pharmaceutically acceptable formulation agent such as carrier such as phosphate buffer, adjuvant, solubilizer such as Tween 80, anti-oxidants such as ascorbic acid, and sodium metafisulfate (See column 11, lines 11-32, in particular). The '784 patent teaches the advantages of N-terminally pegsylated protein are providing a homogeneous preparation to ease in clinical application in predictability of lot to lot pharmacokinetics, for desired dosage, increasing circulation time such as sustained release and resistance to proteolysis and other consideration such as lack of antigenicity (See column 5, lines 29-35, column 6, lines 44-48, column 7, lines 1-5, in particular).

The '038 patent teaches that apoA-I is unstable (see column 2, lines 6-8, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to covalently modified the apo-A-I fragments as taught by Curtis et al using the water soluble polymer as taught by the '784 patent for a water-soluble polymer modified apo-A-I fragments as taught by the '038 patent and the '784 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the '114 patent teaches that Apo-AI-M is useful for protecting subjects from atherosclerosis (See column 1, lines 64-65, in particular). The '038 patent teaches apoA-I is unstable (see column 2, lines 6-8, in particular). The '784 patent teaches that N-terminally pegylated protein provides a homogeneous preparation to ease in clinical application in predictability of lot to lot

pharmacokinetics, for desired dosage, increasing circulation time such as sustained release and resistance to proteolysis and other consideration such as lack of antigenicity (See column 5, lines 29-35, column 6, lines 44-48, column 7, lines 1-5, in particular).

24. Claims 15-16, 38-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No 5,721,114, (Feb 24, 1998, PTO 892) in view of US Pat No. 5,824,784 (Oct 1998; PTO 892).

The teachings of the '114 patent have been discussed supra. The '114 patent further teaches that Apo-AI-M is useful for protecting subjects from atherosclerosis (See column 1, lines 64-65, in particular).

The claimed invention in claims 38, and 39 differs from the teachings of the reference only that composition wherein the pharmaceutically acceptable formulation agent comprises at least one of adjuvant, solubilizer, stabilizer or anti-oxidant.

The claimed invention as recited in claims 40 and 42 differs from the teachings of the reference only that polypeptide is covalently modified with a water-soluble polymer.

The claimed invention as recited in claims 41 and 43 differs from the teachings of the reference only that polypeptide is covalently modified with a water soluble polymer wherein the water soluble polymer is selected from polyethylene glycol, monomethoxy polyethylene glycol, dextran, cellulose, poly(N-vinyl pyrrolidone) polyethylene glycol, propylene glycol homopolymers, polypropylene oxide/ethylene oxide co-polymers, polyoxyethylated polyols and polyvinyl alcohol.

The '784 patent teaches method and composition for covalently modified any polypeptide of interest such as G-CSF or INF with a water-soluble polymer such as polyethylene glycol, monomethoxy polyethylene glycol, dextran, cellulose, poly(N-vinyl pyrrolidone) polyethylene glycol, propylene glycol homopolymers, polypropylene oxide/ethylene oxide co-polymers, polyoxyethylated polyols and polyvinyl alcohol (See abstract, column 6, lines 32-67 bridging column 7, lines 1-5, column 9, lines 64-66, in particular). The '784 patent further teaches pharmaceutically acceptable formulation agent such as carrier such as phosphate buffer, adjuvant, solubilizer such as Tween 80, anti-oxidants such as ascorbic acid, and sodium metafisulfate (See column 11, lines 11-32, in particular). The '784 patent teaches the advantages of N-terminally pegsylated protein are providing a homogeneous preparation to ease in clinical application in predictability of lot to lot pharmacokinetics, for desired dosage, increasing circulation time such as sustained release and resistance to proteolysis and other consideration

such as lack of antigenicity (See column 5, lines 29-35, column 6, lines 44-48, column 7, lines 1-5, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to covalently modified the allelic variant apo-A-I fragment as taught by the '114 patent using the water soluble polymer as taught by the '784 patent for a water-soluble polymer modified apo-A-I fragments as taught by the '038 patent and the '784 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the '114 patent further teaches that Apo-AI-M is useful for protecting subjects from atherosclerosis (See column 1, lines 64-65, in particular). The '784 patent teaches that N-terminally pegylated protein provides a homogeneous preparation to ease in clinical application in predictability of lot to lot pharmacokinetics, for desired dosage, increasing circulation time such as sustained release and resistance to proteolysis and other consideration such as lack of antigenicity (See column 5, lines 29-35, column 6, lines 44-48, column 7, lines 1-5, in particular).

25. No claim is allowed.

26. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (703) 872-9306.

27. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Phuong N. Huynh, Ph.D.
Patent Examiner
Technology Center 1600
March 22, 2004

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Notice to Comply	Application No.	Applicant(s)	
	Examiner Phuong N. Huynh	Art Unit 1644	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☒ 7. Other: SEQ ID NO: is required for FIG. 1C and FIG. 1D

Applicant Must Provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

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